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| 10/568,329 | 02/15/2006 | Gunter Stempfer | BPG33319ASZB | 2915 |
| 72554 | 7590 | 03/09/2010 | EXAMINER | |
| SANDOZ INC 506 CARNEFIE CENTER PRINCETON, NJ 08540 | | | NGUYEN, QUANG | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1633 | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--|--|--|
| Office Action Summary | Application No. 10/568,329 | Applicant(s) STEMPFER ET AL. | |
| | Examiner QUANG NGUYEN, Ph.D. | Art Unit 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 10-12 and 16-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 10-12, 16-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>9/30/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed on 12/14/2009 has been entered.

Amended claims 1, 10-12, 16-22 are pending in the present application and they are examined on the merits herein.

Response to Amendment

The prior art rejections that were set forth in the Office action mailed on 7/14/2009) were withdrawn in light of Applicant's amendment (please see at least amended independent claim 1 with all new limitations).

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1, 10-12 and 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended independent claim 1 recites the limitations "**interrupting fermentation of the host cell in the fermentation prior to completion of the fermentation**",

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“concentrating the fermentation medium by centrifugation or micro filtration prior to and/or in conjunction with interruption of the fermentation”. The as-filed specification **does not have a written support for these new limitations** in the method as now claimed. While the as-filed specification has support **for interrupting the isolation process after fermentation** and put on hold the further processing of the fermentation harvest broth before the subsequent steps of extraction and isolation of a recombinant polypeptide are performed (see at least page 4, last paragraph; page 5, third paragraph; page 6, fourth and fifth paragraphs; page 7, second paragraph; and examples 1-3), it does not teach or even suggest any concept that fermentation is terminated prematurely or not allowed to go to completion. Additionally, the as-filed specification only has the support for the step of concentrating the fermentation harvest broth **before OR after** the interrupting step (see page 10, second paragraph); and not in conjunction (at the same time or simultaneously or concurrently) with the interrupting step. In the amendment filed on 12/14/09 (page 5), Applicants simply stated that support for the amendments may be found in the original claims and in the specification, without citing any specific page and/or line numbers. It is noted that at least original claim 1 recites **“b) interrupting the further processing of the fermentation harvest broth, and maintaining it under defined conditions of temperature and pH prior to extract”**. It is apparent that neither the original claim 1 nor its dependent claims has the support for the concept of interrupting fermentation of the host cell in the fermentation medium prior to completion of the fermentation. Thus, there is **no written support** in the originally filed specification for the method as presently claimed.

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Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate and/or had possession of the instant claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1, 10-12, 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for a process of preparing a recombinant polypeptide as claimed for the reasons discussed below.

1. *The breadth of the claims*

The claims are directed to a method for preparing any recombinant polypeptide comprising the step of interrupting fermentation of any prokaryotic host cell comprising a periplasm in the fermentation medium **prior to completion of the fermentation** and maintaining the host cell on hold in the medium under non-lethal conditions as recited in step (b) of independent claim 1, **wherein the yield of polypeptide recovered from the periplasm is increased compared to the polypeptide yield of processes in which fermentation is not interrupted, but is instead taken to completion.** Please note that the claims encompass a method in which fermentation can be carried out for any period of time (e.g., 5 minutes, 1 hour, 3 hours or 10 hours) as long as the fermentation does not go to completion.

2. *The state of the prior art and the unpredictability of the prior art*

At about the effective filing date of the present application (08/20/2003), virtually nothing was known in the prior art for a process of preparing a recombinant polypeptide having the steps recited in claim 1 as evidenced at least by the teachings of Bochner et al (US 4,680,262; IDS), Hauptmann et al (US 5,710,027; IDS) and Hart et al (Bio/Technology 12:1113-1117, 1994; IDS). Moreover, Donovan et al (Journal of Industrial Microbiology 16:145-154, 1996; IDS) already reviewed a wide variety of factors which influence the expression of foreign proteins under the control of the *lac* promoter in *Escherichia coli*, let alone for the expression of any recombinant polypeptide under any other expression system in any other prokaryotic host cell

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containing a periplasm. Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03).

3. *The amount of direction or guidance provided*

Apart from a surprising disclosure that the yield of a recombinant polypeptide expressed *in E. Coli* is increased **by interrupting the isolation process after fermentation** and put on hold the further processing of the fermentation harvest broth before the subsequent steps of extraction and isolation of the recombinant are performed (see examples 1-3), the instant specification fails to provide any guidance for a skilled artisan on how to obtain an increased yield of a recombinant polypeptide from a method in which fermentation can be carried out for any period of time (e.g., 5 minutes, 1 hour, 3 hours or 10 hours) as long as the fermentation does not go to completion compared to the polypeptide yield of processes in which fermentation is taken to completion, in the method as claimed. How is it possible that the expression and yield of a recombinant polypeptide from a fermentation harvest broth taken to completion (e.g., after a 20 hour fermentation) be less than the expression and yield of the same recombinant polypeptide from a fermentation harvest broth derived from an incomplete fermentation (e.g., after a 5 minute fermentation), even the later fermentation harvest broth is subjected to an interruption step in the method as claimed? This is against all scientific rationale and knowledge known in the prior art. There is no factual evidence of record indicating that the recited increased yield of a recombinant polypeptide resulting from the claimed method was actually obtained. Throughout the as-filed specification and including examples 1-3, **the isolation**

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process after fermentation is interrupted and not the fermentation process itself

(see at least page 4, last paragraph; page 5, third paragraph; page 6, fourth and fifth paragraphs; page 7, second paragraph; and examples 1-3). Examples 1-3 also indicated clearly that the observed increased recombinant polypeptide extraction yield is a result of subjecting an isolated cell paste to an interruption step relative to an isolated cell paste not subjected to the same interruption step, and wherein both isolated cell pastes are obtained from a harvest cell broth undergone and completed the same fermentation process. This is supported at least by the following statements “**After fermentation** of the humanized Fab’ producing E. coli K12 strain the harvest broth is clarified by centrifugation (Westfalla CSC6 disk separator, 100 L/h, 15000xg), then **the isolated cell paste resuspended immediately or after a specified interruption period** (time, temperature, wet weight consistency) with extraction buffer (200 mM TRIS/HCl pH 7.4, 20 mM EDTA) to the original harvest volume (final concentration 100 mM TRIS/HCL, 10 mM EDTA) and each preparation extracted 30 min at 25 °C.” (page 14, second paragraph). Furthermore, it is also noted that the mechanism or factors responsible for the increased yield of the recombinant polypeptide in the exemplifications is not fully understood.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the state of the relevant art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633